Perspectives in Regulating Human Cells and Tissues

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Driving Forces & Challenges

- Previous approach (pre 1997) fragmented and inadequate
- New products (e.g, stem cells, tissue-engineered)
- New manufacturing technologies, degree of manipulation
- Increasing public health concern
- Increasing demand for cells and tissues
- Resource limitations
- Public confidence in products - expectation for safe & effective product
- Industry standards not always followed, not enforceable

Cells and Tissues - Examples

- musculoskeletal tissue
- ocular tissue
- dura mater
- human heart valves
- reproductive tissue
- hematopoeitic stem cells
- cellular therapies
- manipulated cells and tissue
- genetically modified cells
- tissue/ cell combined w / device, biologic, drug

Cell and Tissue Characteristics

- Autologous vs. Allogeneic
- Viable vs. Nonviable
- Banked vs. Unbanked
- Homologous vs. Non-homologous function
- Minimal vs. More than minimal manipulation
- Structural vs. Systemic function
- Combination product – device, biologic or drug

Overall CBER Approach to Product Development and Regulation

- GOAL: Balanced, flexible, responsive regulatory approach
  - Assure the safety and rights of subjects
  - Protect the public health
  - Not impede technological innovation & product development
- Influences
  - Available scientific knowledge, pre-clinical, clinical knowledge & experience
  - Crises/ tragic events
- Appropriate timing to develop policy, especially written policy
- **Appropriate Risk Assessment**

FDA Approach to Regulation of Cellular and Tissue-based Products

- Human cells, tissues, or cellular or tissue-based products **(HCT/P's)**[1]
  - Articles containing human cells or tissues that are intended for transplantation, infusion or transfer into a human recipient
- Provides a unified, comprehensive regulatory framework
- Provides a tiered regulatory approach
  - level of regulation proportional to the degree of risk

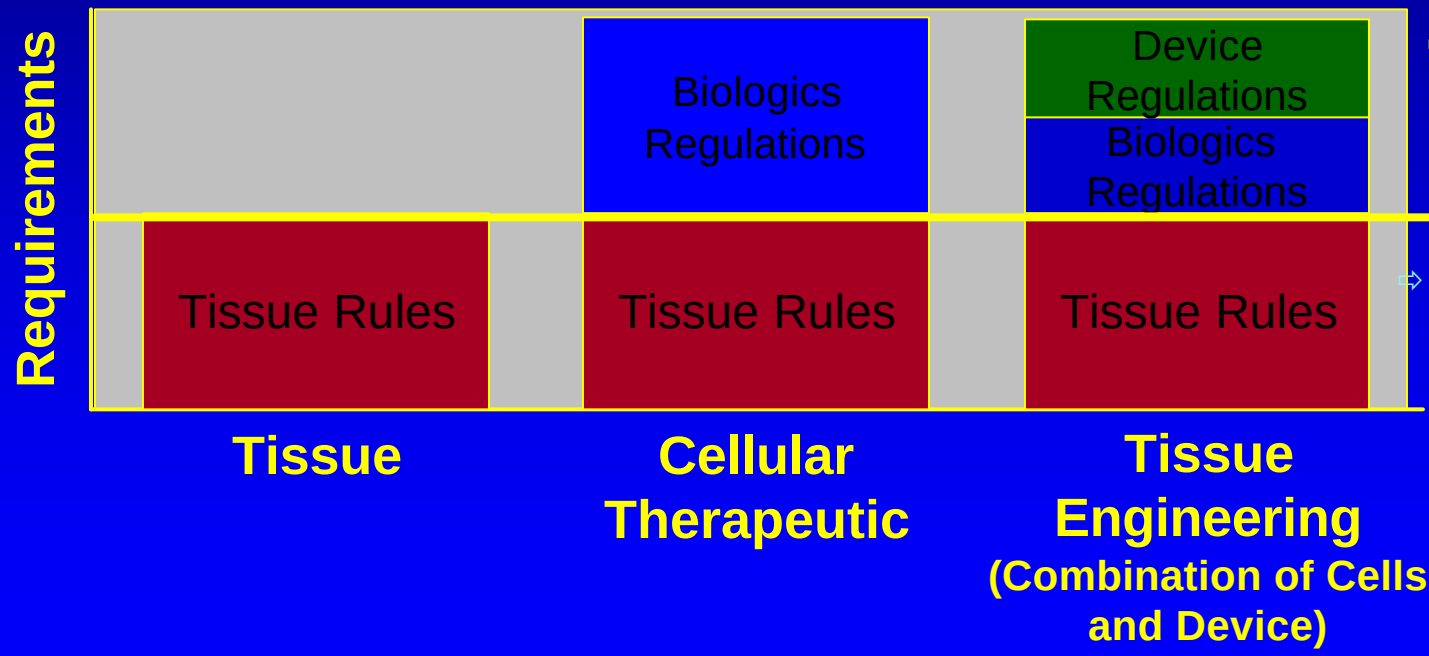
ascularized organs, allogenic bone marrow transplantation, regulated by other Fed
encies; transfusable blood/ blood components, xenotransplantation regulated by F
t under other approaches.

Major Areas of Regulatory Concern

- Prevent use of contaminated tissue the can transmit infectious disease
- Prevent improper handling/ processing that might contaminate or damage tissue
- Demonstrate clinical safety and efficacy, where appropriate

- *Promotional claims*
- *Monitoring of industry*

Regulatory Requirements for HCT/P's



HCT/P's Intended For Transplantation

- Generally, HCT/P's recovered, processed, stored, or distributed by methods not intended to change tissue function or characteristics
- Minimally manipulated, homologous use, metabolic tissue for self or close blood relative, or for reproductive use
- Regulated only under communicable disease provisions - section 361 of PHS Act ("361 HCT/P's")
  - Comply with "Tissue Rules"
  - Premarket submission or approval not needed

HCT/P's Regulated as a 351 Product, i

1) More than minimally manipulated
2) Intended for Non-Homologous Use (non-normal function)
3) Systemic effect dependent upon metabolic activity
   - Unless autologous use, allogenic use isn 1st or 2nd degree relative, or reproductive use
4) Clinical effect is systemic or dependent upon the metabolic activity of the cells for its primary function
5) Combined with a device, drug or biologic
   - Unless it is a sterilizing, preserving, or storage agent with no new clinical safety concerns?

Exception - cells and tissues are not regulated if they are removed from and returned to the patient in the same surgical procedure

HCT/P's Regulated as Biologics or Devices

- More stringent safety and efficacy provisions of PHS Act ("351 HCT/P's") and FDC Act
  - Comply with Tissue Rule
  - Premarket review required – controlled clinical trials needed to demonstrate safety and efficacy.

Examples of HCT/P's & Regulatory Oversight

enerally Regulated Under Section 361 PHSAct

- musculoskeletal tissue
- ocular tissue
- dura mater
- human heart valves
- reproductive tissue
- hematopoeitic stem cells

Regulated Under Section 351 PHSA, FDCAct

- cellular therapies
- manipulated cells and tissue
- genetically modified cells
- tissue/ cell combined w / dev biologic, drug

Rule Governing HCT/P's Intended For Human Transplantation

14 Oct 1993
Application of Current Statutory Authorities to Human Somatic Cell-Therapy and Gene-Therapy Products
58 FR 53248

4 Mar 1997
A Proposed Approach to the Regulation of Cellular- and Tissue-Based Products
62 FR 9721

20 May 2004 Eligibility Determination for Donors of Human Cells, Tissues, and Cellular Tissue-Based Products
69 FR 29785

1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005

14 Dec 1993
Human Tissue Intended for Transplantation
58 FR 65514

19 Jan 2001
Human Cells, Tissues, and Cellular- and Tissue-Based Products; Establishment Registration and Listing
66 FR 5447

25 May 2005
Current Good Tissue Practice for Manufacturers of Human Cellular- and Tissue-Based Products; Inspection and Enforcement
66 FR 1508)

Establishment Registration and Listing

- Requires establishments to register with FDA and list HCT/P's
  - Exclusions for some (e.g.,storage, carriers, contractors engaging only in recovery and transport)
- Lists criteria to determine if HCT/P's regulated solely under 361 PHSAct

Donor Eligibility

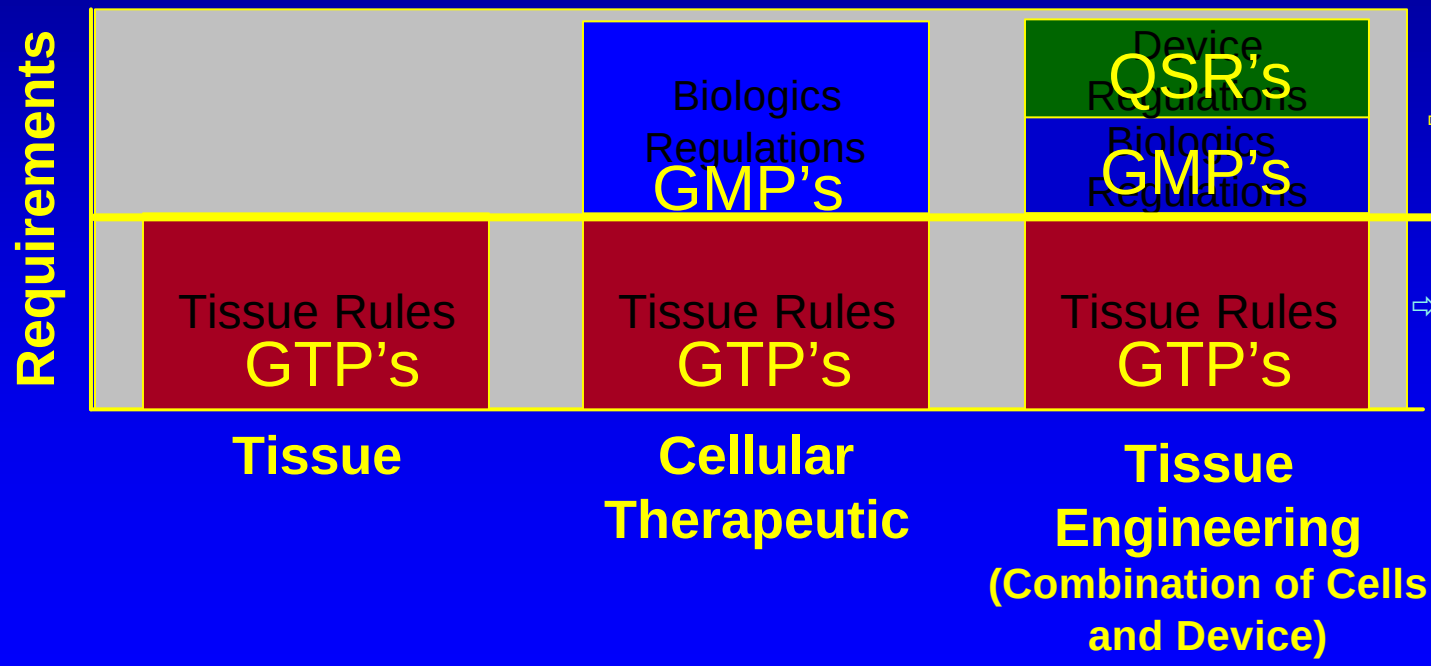
- Screening and testing of most cell and tissue donors for relevant communicable diseases
  - Exception for autologous donor/ sexually intimate partner
- Donor must be eligible prior to HCT/P administration
  - Free of risk factors & clinical evidence of communicable disease
  - Acceptable test results
  - Limited exception to use when eligibility determination not completed
    - ☞– urgent medical need, w/o other comparable HCTP available
  - Limited use of HCT/P from an ineligible donor

Good Tissue Practices

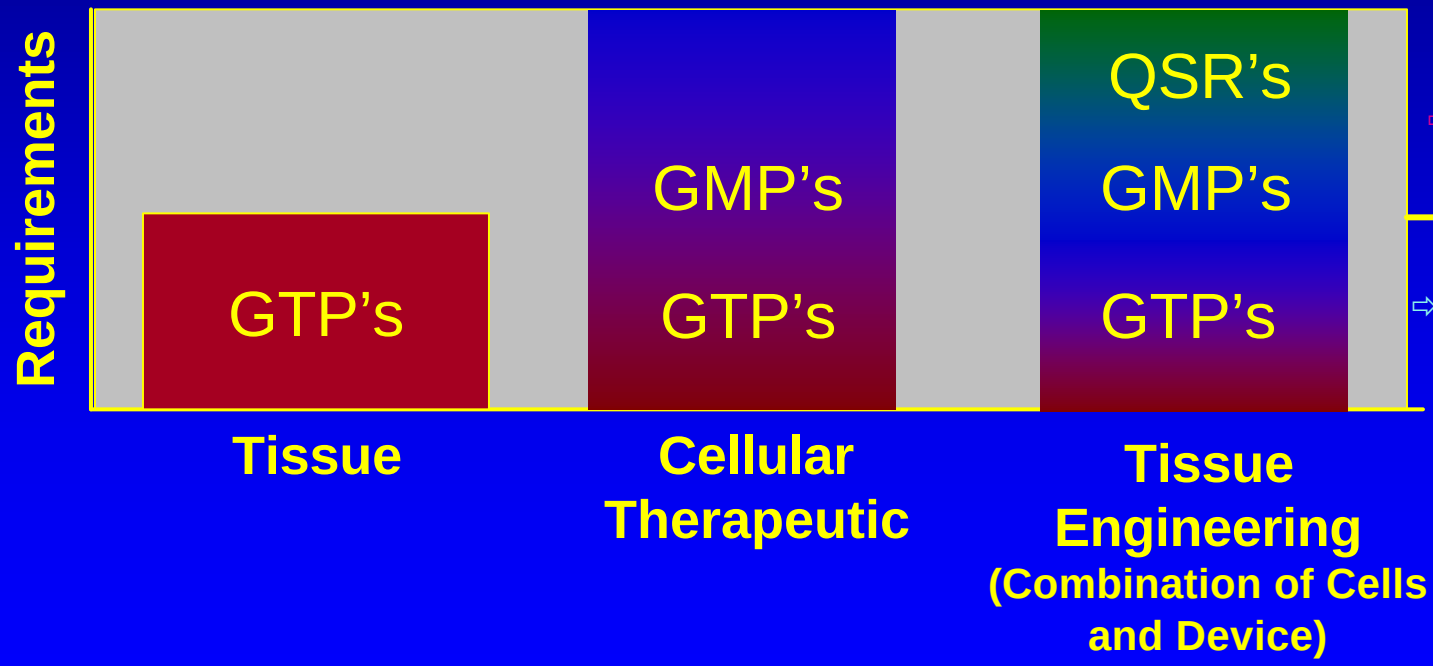
(Applicable to products after May 25, 2005)

- Procedures and controls to prevent introduction, transmission and spread of communicable disease by HCT/P's
  - communicable disease agents – prior to and during manufacturing
- Organized around core requirements, with supporting requirements
  - Follow all GTP requirements applicable to function performed
  - Requirement for a Quality Program
- Flexibility to determine how to meet requirements

Regulatory Oversight & Requirements for HCT/P's



Practical Relationship Among Regulatory Requirements



Advantages of FDA Approach

- Risk - based – proportionate regulation
- Consistent & predictable treatment
- Provides clear, enforceable standards
- Provides public confidence, supports innovation
- Provides placement for new products

Challenges

- Tissues
  - Adventitious Agents
  - Contamination, Detection, Quantitation
  - Inactivation Methods
- Hospital-based treatments

Challenges - Somatic Cellular Therapies/ Combination Products

- Demonstration of Safety and Efficacy
  - Mechanisms of Product Toxicity
- Product Characterization and Testing
  - Testing technologies, Assay Variability, Relevant Criteria
- Manufacturing
  - Ancillary Products, Standards
  - Consistency, Process Validation
- Imagination and creativity in development and application of new technologies and products

Critical Path Initiative

- CBER Historical Legacy
  - CBER conducted research and studies on overall quality and specific problems related to development, manufacture and testing of biologics -
  - CBER closely interacts (“Partner”) with developers of products
- Critical Path Initiative (FDA Initiative)

International Activities

- ICDRA Recommendations [February, 2004]
  - Develop and Implement effective national regulation
  - WHO should develop of Quality, Safety and Efficacy guidelines
  - WHO should facilitate surveillance – written standards and reference materials
- WHA Resolution - [adopted May 2004]
  - Allogenic Transplantation
  - Implement effective national oversight – accountability and traceability
  - Harmonize practices - Procure, process, transplantation
  - Considerations for ethical issues
  - Policing sales and trafficking in human organs and tissues

CBER Available Documents

- Office of Cellular, Tissues and Gene Therapies
  - Tissues - Ruth Solomon
  - Cellular Therapies – Kimberly Benton
- Guidance/ Information
  - www.fda.gov/cber
  - Manufacturers assistance:OCTMA@cber.fda.gov